REMARKS

The Office Action dated April 9, 2004, has been received and reviewed. Claims 1-22 are pending in the present application. Claims 3-22 have been withdrawn from consideration by the Examiner as being drawn to a non-elected invention. Applicants note that with respect to Claims 3-22, Applicants noted that these claims were withdrawn **with traverse** in the last response. *See*, Office Action of October 30, 2003, page 9 of 11. Applicants also note that during the interview with the Examiner this election was made with traverse. Applicants further note that restriction was traversed on the basis that the claims are directed to the same polymorphism and thus would not require any additional search on the part of the Examiner.

Claims 1-2 stand rejected. Claim 1 has been amended to recite a human female. Claims 1 and 2 have been amended to remove the phrase "the rare form". Claims 23-26 have been added to depend from claim 1. Support for these claims can be found in paragraphs 29-31 and throughout the application. Applicants respectfully request reconsideration of the application in view of the amendments to the claims and the arguments below.

I. Objections to Specification

The specification has been objected to as allegedly not properly incorporating documents by reference, focusing on pages 5, 6 and 9. Applicants respectfully disagree with this assertion. Applicants note that with respect to matters for an enabling disclosure which are not common or well known, an applicant may, in the interests of economy of time and space, incorporate certain types of documents by specific reference in his application to such source materials. *See, In re Howarth*, 654 F.2d 103, (CCPA 1981). After ruling that prior U.S. patents may be so incorporated, *In re Stauber*, 18 CCPA 774, 45 F.2d 661, 7 USPQ 258 (1930), the federal courts extended the doctrine of incorporation by reference stating as a general guideline in *In re Heritage*, 37 CCPA 1109, 1115, 182 F.2d 639, 643, 86 USPQ 160, 164 (1950), that "any reference to a disclosure which is available to the public is permissible." *Id.* Furthermore, under 37 C.F.R. § 1.71(a) "[t]he specification must include a written description of the invention or discovery and of the manner and process of making and using the same, and is required to be in such full, clear, concise, and exact terms as to enable any person skilled in the art or science to which the invention or discovery appertains, or with which it is most nearly connected, to make and use the same." The present specification meets these requirements. Applicants note that

page 5 recites that "[t]he nucleotide sequence of human estrogen receptor alpha is known and suitable probes, restriction enzyme digestion techniques, or other means of detecting the polymorphism may be implemented based on this known sequence in accordance with standard techniques. *See, e.g.,* U.S. Patent Nos. 6,027,896 and 5,767,248 to A. Roses et al." These patents are cited for the purpose of illustrating to one of skill in the art the ability to detect a polymorphism based upon techniques known in the art thus meeting the federal requirements. Applicants further note that on page 6 it is recited that "[n]umerous different oligonucleotide probe assay formats are known which may be employed to carry out the present invention. See, e.g., U.S. Pat. No. 4,302,204 to Wahl et al.; U.S. Pat. No. 4,358,535 to Falkow et al.; U.S. Pat. No. 4,563,419 to Ranki et al.; and U.S. Pat. No. 4,994,373 to Stavrianopoulos et al." Again, one of skill in the art can look to these patents and readily discern how to use an oligonucleotide probe assay to carry out the present invention. Furthermore, page 9 recites that [n]umerous estrogen replacement therapy preparations and protocols are known, including but not limited to those described in U.S. Patents Nos. 5,922,349; 5,897,539; 5,565,199; 5,468,736; 5,422,119; 5,288,717; and 5,023,084. These patents are not mere references to an abandoned application as indicated in emphasis by the Examiner, but actual patents which <u>are available to the public</u> and which one of skill in the art would be able to make and use the same. Applicants note what is well settled is that the specification must set forth the precise invention for which a patent is solicited, in such manner as to distinguish it from other inventions and from what is old. It must describe completely a specific embodiment of the process, machine, manufacture, composition of matter or improvement invented, and must explain the mode of operation or principle whenever applicable. See, 37 C.F.R. § 1.71(b). Applicants further note that the present Examiner has allowed numerous cases of incorporation by reference wherein no reason for the listing of the reference is given or the references are listed for the purpose of protocols or methods known in the art. See, U.S. Patent Nos. 6,656,684 6,617,439 and 6,586,234. Accordingly, Applicants respectfully request reconsideration and withdrawal of the objections to the specification.

Applicants have further amended paragraph 58 to include the trademark as requested by the Examiner. Accordingly, Applicants respectfully request reconsideration and withdrawal of the objections to the specification.

II. Priority

Applicants respectfully disagree that the provisional application fails to provide adequate support for Claims 1 and 2 of the present application. Applicants note the specification of the provisional application clearly describes polymorphisms that provide a favorable indication of response to estrogen replacement therapy including the PvuII and XbaI polymorphisms, which as noted in the present specification in paragraph 29, "[f]or IVS1-401/PvuII the rare allele is C. For IVS1-354/XbaI the rare allele is G." Applicants further direct the Examiner's attention to page 4 of the provisional application and paragraphs 30 and 31 of the present specification to note the additional polymorphisms claimed in both the provisional and present applicaiton. Accordingly, the note that the priority fails to provide adequate support is in error and Applicants request that such claim be removed.

III. Claim Rejections

A. 35 U.S.C. §112, first paragraph, written description

Claims 1-2 stand rejected as allegedly failing to comply with the written description requirement. Applicants respectfully disagree with this assessment as one of skill in the art could readily determine if a subject has the polymorphism disclosed. However, in an effort to expedite the present application, Applicants have amended the claims utilizing the language suggested by the Examiner and have recited "female humans" rather than "subject". Accordingly, Applicants respectfully request reconsideration and withdrawal of the written description rejections of Claims 1-2.

B. 35 U.S.C. §112, first paragraph, enablement

Claims 1 and 2 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. Applicants respectfully traverse this rejection.

Applicants note that the "test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." (MPEP §2164.01, citing *In re Wands*, 858 F.2d 731, 737). Furthermore, the test for whether or not the enablement requirement has been met involves determining whether or not practice of the invention as claimed involves "undue experimentation". It has long been settled that "the key word is 'undue', not 'experimentation'".

In re Angstadt, 190 USPQ 214, 219 (C.C.P.A. 1976). In the present case, Applicants submit that the application of the current technology requires routine effort, and not undue experimentation. Applicants further note that they have amended the claims to recite that the method of screening is for human females. The Office Action alleges that the present specification has not provided evidence that the presence of these polymorphisms are found in other life forms, and that any of them has been shown to correlate with improved cardiovascular disease in women. Applicants note that the specification discloses that homozygotes for the less common intron 1 alleles experienced a 24% to 33% increase in HDL with HRT compared with a 13% increase in carriers of more common alleles. *See,* Paragraph 67. Furthermore, baseline HDL levels were slightly higher in IVS1-401 C/C and IVS1-1505 G/G women compared with women with the IVS1-401 T/T and IVS1-1505 A/A genotypes, respectively (P = 0.052 and 0.063). *See,* Paragraph 67. Additionally, in women on hormone replacement therapy with the IVS1-401 C/C genotype, HDL_3 levels increased by 13.6 mg/dl compared with 8.2 mg/dl in women with the C/T or T/T genotypes (P for interaction = 0.04). *See,* Paragraph 67 and Figure 3. Applicants further note that Table 2 provides evidence for a human female having an ERα polymorphism having a favorable response to HRT. Applicants further note that the claims are directed to specific polymorphisms and not any polymorphism as suggested by the Examiner. Furthermore, again Applicants note that it is well known in the art that an increase in HDL levels is favorable for cardiovascular health. Accordingly, Applicants submit that one of skill in the art could readily practice the invention as presently claimed in the application. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejections to Claims 1 and 2.

C. 35 U.S.C. §112, second paragraph

Claims 1 and 2 also stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Office Action alleges that the claims are indefinite as to what "constitutes 'the rare form' of the polymorphism. Applicants note that throughout the specification that the rare form of estrogen receptor alpha polymorphisms is disclosed, and in particular these disclosures include the rare form of polymorphisms found in the first intron of the estrogen receptor alpha gene. However, in an effort to expedite the present matter, Applicants have amended Claims 1-2 to remove "the rare form". Applicants have also added

Claims 23-26 to further illustrate the polymorphisms disclosed in the present application. Accordingly, Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. § 112, second paragraph rejections to Claims 1 and 2.

CONCLUSION

In view of the remarks presented herein, Applicants respectfully submit that the claims define patentable subject matter. If, in the opinion of the Examiner, a telephonic conference would expedite the examination of this matter, the Examiner is invited to call the undersigned attorney at (919) 854-1400.

It is not believed that an extension of time and/or additional fee(s)-including fees for net addition of claims-are required, beyond those that may otherwise be provided for in documents accompanying this paper. In the event, however, that an extension of time is necessary to allow consideration of this paper, such an extension is hereby petitioned under 37 C.F.R. §1.136(a). Any additional fees believed to be due in connection with this paper may be charged to our Deposit Account No. 50-0220.

Respectfully Submitted,

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